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Implementation of mechanism of action biology-driven early drug development for children with cancer

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Implementation of Mechanism of Action biology-driven early drug development for children with cancer

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The need for new drugs for children with cancer is greater than ever. A Paediatric Platform is being established to implement a mechanism of action model of early drug development, rather than following the adult indications, by matching an aggregated biological database of paediatric tumours with an aggregated drug pipeline. This is a new paradigm that should allow early evaluation of new drugs in children and adolescents.

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Abstract

An urgent need remains for new paediatric oncology drugs to cure children who die from cancer and to reduce drug-related sequelae in survivors. In 2007, the European Paediatric Regulation came into law requiring industry to create paediatric drug (all types of medicinal products) development programmes alongside those for adults. Unfortunately, paediatric drug development is still largely centred on adult conditions and not the mechanism of action (MoA)-based model, even though this would be more logical for childhood tumours as these have much fewer non-synonymous coding mutations than adult malignancies. Recent large-scale sequencing by ICGC (International Genome Consortium) and PCGP (Pediatric Cancer Genome Project) has further shown that the genetic and epigenetic repertoire of driver mutations in specific childhood malignancies differs from more common adult-type malignancies. To bring about much needed change, a Paediatric Platform, ACCELERATE, was suggested in 2013 by the Cancer Drug Development Forum (CDDF), Innovative Therapies for Children with Cancer (ITCC), the European Network for Cancer Research in Children and Adolescents (ENCCA) and the European Society for Paediatric Oncology (SIOPE). The Platform, comprising multiple stakeholders in paediatric oncology, has three Working Groups (WG), one with responsibility for promoting and developing high-quality MoA-informed paediatric drug development programmes, including specific measures for adolescents. Key is the establishment of a freely accessible aggregated database of paediatric biological tumour drug targets to be aligned with an aggregated pipeline of drugs. This will enable prioritization and conduct of early-phase clinical paediatric trials to evaluate these drugs against promising therapeutic targets and to generate clinical paediatric efficacy and safety data in an accelerated time-frame. Through this work, the Platform seeks to ensure that potentially effective drugs, where the MoA is known and thought to be relevant to paediatric malignancies, are evaluated in early phase clinical trials, and that this approach to generate pre-clinical and clinical data is systematically pursued by academia, sponsors, industry and regulatory bodies to bring new paediatric oncology drugs to front-line therapy more rapidly.

Introduction

Survival rates for children with cancer increased from 20% to 80% between the 1960s and 1990s (Craft and Pearson 1990, Rössig 2013). Disappointingly this progress has not continued and improvements have plateaued over the last 25 years optimising conventional therapies as undertaken in high-income countries (Pritchard-Jones K, 2013), with children and young people not benefiting from the current expansion in targeted, mechanism of action (MoA)-based therapies in adults. Twenty percent of children with cancer still die from this disease in Europe and North America, with the outcomes for high-risk neuroblastoma, high-risk medulloblastoma, metastatic sarcoma, bone tumours, high-risk ependymoma, and high-grade glioma remain very poor. Furthermore, 40% of survivors live with disabling sequelae through adulthood (Vassal 2013a). In part this lack of progress can be attributed to sub-optimal methods of paediatric oncology drug development, which largely continue to be driven by drug development for adult cancers. There is also an unjustified adherence to the separation of adults and minors in clinical trials, despite the known maturation of hepatic and renal systems in older children, with minors at times being excluded from entering “adult” early phase cancer studies, although this has no physiological basis. Additionally, until recently, a ‘silo’ method of working was prevalent amongst the many different groups in the field. However, in all three areas change is manifest.

A force for change has been the European Paediatric Medicine Regulation EC No. 1901/2006 which requires an agreed Paediatric Investigation Plan (PIP) (EMA 2006) to provide data supporting paediatric usage as part of each new adult drug development plan. However, where adult and paediatric diseases (conditions) are not the same, the Regulation allows for waivers of paediatric studies if the disease that the drug is being developed for only occurs in adults.

To accelerate progress, a Paediatric Oncology Platform, ACCELERATE, comprising three Working Groups (WG) was formed in 2013 (Vassal 2015). This paper reports on progress made by one WG in MoA-driven drug development. This represents a paradigm shift that will benefit children and adolescents.

Context/landscape

Paediatric Medicine Regulation and paediatric oncology drug development in Europe

Before the European Paediatric Medicine Regulation No EC 1901/2006 (the Regulation), clinical evaluation of new agents for paediatric and adolescent malignancies was often absent and by necessity drugs were most often used off-label. The Regulation provided obligations and incentives through completing PIPs and in conjunction with the legislation on orphan drugs aimed to facilitate a much-needed change to drive paediatric drug development forward. It sought to ensure that such medicines were developed with high-quality, ethical research in children, without subjecting them to unnecessary clinical trials, but balancing this with the reality and hazards of off-label use, and at the same time ensuring no delays to adult drug development. Thus PIPs became the means by which paediatric drug development was planned based on proposals by pharmaceutical companies, optimal collaboration with academic networks, and agreement by the Paediatric Committee of the EMA (PDCO).

Pharmaceutical companies developing new medicines are legally bound to comply with agreed PIPs to submit the marketing authorisation (MA), but may request a waiver which obviates this requirement. Waivers, if requested, are to be granted because (i) the adult condition on the proposed drug label does not occur in children (e.g., breast cancer); (ii) the drug would likely be unsafe or ineffective in children; (iii) there is no significant therapeutic benefit above existing paediatric treatment. The marketing authorisation of everolimus for subependymal giant cell astrocytoma is a prototype for successful MoA driven drug development in paediatric oncology. Whilst the Regulation has brought positive change and advances, the waiver mechanism means that with over 60% of 89 potentially valuable anticancer drugs granted a waiver (Vassal and Pearson Personal Communication 2015), there are still few paediatric trials and only between 9–15% of all oncology agents have ongoing paediatric studies (Vassal 2013b, FDA Pediatric Oncology Subcommittee of ODAC, November, 2013). Thus many children with cancer continue to have limited options and no access to new therapies.

Although the Regulation already includes the possibility of agreeing PIPs for biology-driven, paediatric development within or outside of that for adults, in truth paediatric drug development is still largely driven by that for adults. From 2008–2012 over 470 PIPs were agreed covering all paediatric therapeutic areas, with 52 PIPs for malignancies being one of the largest areas, but only a few PIPs for cancers that specifically occur in children and adolescents; and only a few were completed by the time of the EMA's 5-year interim report on the Regulation (EMA 2013).

The Paediatric Platform - ACCELERATE

In 2013, the Cancer Drug Development Forum (CDDF), Innovative Therapies for Children with Cancer (ITCC), the European Network for Cancer Research in Children and Adolescents (ENCCA) and the European Society for Paediatric Oncology (SIOPE) suggested creating a Paediatric Oncology Platform comprising representative stakeholders involved in the care of children with cancer – academia, industry, regulatory authorities and parent and patient advocates (Vassal 2015). Its WGs address key aspects of paediatric oncology drug development: (i) New strategies for improved development of oncology drugs for children and adolescents including MoA, biology-driven drug development; (ii): New incentives for specific paediatric drug development and repositioning; (iii) Implementation of long-term follow up measures for children and adolescents receiving new anticancer drugs. Each WG includes representatives from each stakeholder group, but is led by a member with the relevant expertise for the work stream.

MoA biology-driven development

First principles

Core to this approach is discovery and understanding of the molecular pathways, biology and key drivers of paediatric malignancies focussing on gene/pathway aberrations that demonstrate a proof of "tumour dependence", combined with detailed biological insight of a drug's MoA. The paediatric oncology research community through extensive collaboration worldwide has been at the forefront of exploiting next-generation sequencing technologies to gain better insight into tumour biology (Zhang 2013, Hovestadt 2014, Kool 2014, Buczkowicz 2014, Taylor 2014, Wu 2014). Furthermore, it is critically important to realize that the average number of non-synonymous coding mutations in childhood tumours is on average about a

hundred fold lower than in adult malignancies. This means that the likelihood of correctly identifying the “Achilles Heel” of the tumour for targeted therapies is much higher thus comprising a much more promising and clean target population for MoA-based drugs to actually work. With this knowledge, one can take a more systematic approach matching drugs with an identified MoA to a particular disease or across different diseases based on biology. Pre-clinical research varies with different tumour types, and may be limited by availability of tumour samples and/or relevant pre-clinical tumour models; this remains a particular challenge for paediatric cancers. The proposed MoA approach aims to identify appropriate paediatric patient populations to which MoA-driven drug development is applicable.

Broadly, paediatric oncology drugs can be categorised as: i) those for diseases occurring in adults and children, e.g., gliomas and certain haematological malignancies; ii) those targeting a MoA relevant/common to both the intended adult cancer and a distinct/different paediatric malignancy, such as BRAF, e.g., melanoma in adults; high and low grade gliomas and histiocytosis in children, or one different in terms of molecular alteration, such as anaplastic lymphoma kinase [ALK] alterations in neuroblastoma rather than non small cell lung cancer; iii) those against targets specific to, or predominant in, paediatric malignancies, e.g., MYCN, which has not yet been developed as a relevant target in adult cancers. Other targets in this last group are currently being identified from paediatric pan-cancer analyses of next-generation sequencing programmes.

Practicalities of a MoA model

The key elements of a MoA approach are: i) an aggregated database which establishes the incidence and prognostic relevance of tumour targets in paediatric malignancies; ii) appropriate selection of drugs; iii) drug prioritisation; iv) specific pre-clinical and clinical studies (early and late phase clinical trials) (Figure 1).

An iterative, *life-cycle* approach should be adopted for MoA-driven drug development and can be reflected in PIP modifications, with the direction of drug development continually reviewed following evolution of the data and applicable science. The Paediatric Committee is not at liberty to require a MoA-driven development for a childhood cancer that is different from the cancer targeted in adults, or to require PIP

modifications, but has agreed to a number of such proposals by pharmaceutical companies. Currently, PIPs are relatively 'fixed' at the time of their agreement though some include obligations on the part of the PIP addressee (mostly industry) to go back for further review. A systematic life-cycle approach would thus have many advantages, and would be important particularly when multiple companies generate data on the same target and/or in the same class of drug.

(i) Aggregated database of tumour targets

Central to this approach is an aggregated and publicly available database of the critical pathways / drivers in different paediatric and adolescent malignancies, enabling matching of the MoA to a specific disease. The incidence/prognostic relevance in individual malignancies and across cancer types should be included in the database and evidence supporting the strength of the target as a cancer driver. Detailed molecular profiling of tumours both at presentation and relapse will provide information. The incidence of actionable target mutations is the most easily obtained information; determination of the functional relevance of identified targets for tumour cell survival and the relevance of complicated tumour-host interactions is a more challenging task.

The aggregated database will define the non-clinical rationale for choosing a paediatric MoA-informed approach. Drug selection is based on the presence and prioritisation of molecular targets as key drivers, altering clinical outcomes of paediatric malignancies. The database will be used to develop predictive pre-clinical models that recapitulate clinical features of the paediatric tumours. Drug development will be based on targets across tumour types. Due to the distribution of tumour targets, some will predominate in one disease and development of drugs may in practice tend to be led by that tumour type. However, practice should evolve so that the target rather than the histological tumour type defines the medicine used. Such a database will also be crucial when considering treatment combinations.

(ii) Selection of drugs

The goal is to match, as early as possible, the tumour biology, including interaction with the host environment, with drugs already in the development process; this requires alignment of an aggregated pipeline of drugs with an aggregated database

of paediatric tumour targets. Selection of drugs should be based on knowledge of the molecular pathways relevant to paediatric malignancies, not on the wording of the adult disease or condition.

(iii) Drug prioritisation

Prioritised drugs from a co-ordinated pipeline of agents should target strong drivers in paediatric malignancies where there are unmet needs. Prioritisation could be informed by structured overviews of the pre-clinical biological knowledge in paediatric malignancies and of the gene/pathway aberrations matching the MoA of the drugs. Drugs which "fit" with paediatric biological tumour targets will then undergo detailed evaluation comprising a review of treatment strategies, regulatory incentives and obligations, molecular mapping within the oncology portfolio and proof-of-concept studies in relevant paediatric preclinical models. This will enable the best-informed selection and timing of medicines for studies and avoid duplication.

Novel drugs with a similar MoA can then be "compared" in a non-competitive space, such that precious resources are not wasted, and paediatric patients are not enrolled on sub-optimal clinical studies unlikely to benefit them. However, this process involving multiple stakeholders will involve significant challenges. Accordingly, this ability to compare mechanisms, efficacy and toxicity profiles, and match rare children to the best available experimental therapy requires further discussion with academia, pharmaceutical industry partners as well as with regulatory authorities.

(iv) Studies

Pre-clinical studies

In view of the large number of compounds of the same class available from different pharmaceutical companies, pre-clinical proof-of-concept research is advocated to adequately prioritize them through pre-competitive multi-company integration. This should ideally include non-clinical safety evaluation, dosing schedule determination, combination testing and mechanism of resistance-analysis, as well as cross-company comparison of non-clinical efficacy, based on molecular mechanisms (for instance ALK translocations versus mutations).

Non-clinical studies exploring the toxicities of these targeted therapies in juvenile animals should enable detection of their potential negative impact on the function or development of major organs in children. Key issues are the secondary pharmacological properties of these drugs, which are not always well understood. These studies also enable the detection of unexpected or exacerbated toxicities when compared with adult animals. Key issues are higher exposure levels linked to immature pharmacokinetics in the younger populations (often metabolic or renal clearances) or toxicities affecting immature organs.

Selection of the *right* drug(s) for clinical evaluation is needed, for which factors such as safety and posology are important considerations.

Clinical studies - early phase clinical trials

Early phase (including first-in-child) clinical trials in a MoA approach should have a clinically relevant, biology-driven hypothesis, be feasible and encompass Phase I (dose-finding and toxicity) and II (proof-of-concept) elements and include expansion cohorts as necessary. The objective is to efficiently and rapidly determine the paediatric recommended Phase II dose (RP2D), toxicity, pharmacological profile and activity signals aiming for optimal biological dose and not MTD. As therapeutic intent is key to the design of such studies in children, appropriate stopping rules, a shift towards more effective therapies, early introduction of combination therapy and innovative designs should be considered.

An early phase clinical study should be initiated once there is a strong biological rationale for a drug targeting a molecular pathway driving the malignancy and as soon as a feasible trial can be designed and deliverable within an acceptable timescale (two years). As a rule, as soon as the adult RP2D has been determined (early phase), paediatric studies should commence as this time point is supported in the regulation for PIP applications. There is a role for very early evaluation of some drugs in children if there is a strong biological rationale, even before therapeutic trials in adults.

It is recommended that any early phase paediatric clinical study with a new medicine should be scientifically optimised to progress drug development and disease

knowledge. Regulators are involved in clinical trial authorisation and should participate in scientific dialogue because of added value from their scientific experience across medicine pipelines. Lack of agreed PIPs does not prevent early clinical trials in children, but discussions of a PIP or scientific advice should take place with regulators to avoid trials that are unnecessary or not useful. Evolving data should inform later stages of drug development. To develop drugs for paediatric indications that are unrelated or "outside" an adult condition for which there is a medicine authorised or in development, a PIP may still be proposed and agreed, thereby giving companies the potential for access to the reward related to compliance with progressing and completing such a programme.

Experience and evidence have shown that unacceptable toxicity is rarely seen in paediatric studies at 100% adult RP2D (Paoletti, 2013). It is therefore now proposed to start at 100% of exposure at the adult RP2D adjusted for body surface area (unless there is a good reason not to do so) and to predict the exposure from modelling physiological and adult data. Special attention should be paid to anticipate more severe toxicity in very young children with immature organ function (in particular those less than 2 to 3 years of age). Mixed criteria for toxicity and efficacy (including the optimal biological dose) should be employed to establish the RP2D. Ideally, the selected dose will be based on determining on-target activity measurements of the compound or non-maximum tolerated dose optimization strategies. Multi-arm designs ("matrix" trials) (Middleton, 2015) should be used in early and later paediatric trials, where feasible. Predictive biomarkers to aid patient selection are important in some studies when there is an actionable mutation, however they may not be available nor validated when starting a first-in-child trial. In addition tumour clonal evolution and tumour heterogeneity should be considered.

There should be a collection of (ideally, fresh frozen) tumour material at the time of enrolment in a study and/or at relapse in order to run biologically well informed trials with knowledge of the current biological status of the tumour and so not rely on archived material, which may lead to incorrect conclusions if the tumour has developed new genetic aberrations over time; a phenomenon known to be true in an increasing number of tumour types including neuroblastoma and medulloblastoma (Schleiermacher, 2014; Hill, 2015). It is also critical that this tissue is assessed in

comparison with biopsies obtained at diagnosis, to address the issue of tumour heterogeneity/clonal evolution. Although sequential tumour samples are of significant value, they may not always be feasible. The role of *liquid* biopsies, e.g., circulating DNA obtained from blood samples, should be considered as well; the use of these could also reduce the trial-related burden for the patients. Furthermore, studies of these tumour samples will reveal resistance mechanisms and provide a rational basis for combination therapies.

Consultation on design of early and subsequent clinical trials should be timely and detailed, and involve contributions from academia, industry, regulators, older children/adolescents and patient/parent advocates and representatives. Academia should participate from the outset, as pivotal information regarding adaptation to improving outcomes in paediatric malignancies (such as addressed in a PIP), as well as expert advice on feasible trial designs, can be obtained through this source. Scientific advice (as part of a PIP or as a specific procedure) can also be obtained from regulators based on their extensive review of medicines and scientific experience across pipelines. In order to facilitate planning of regulatory discussions in initiating clinical trials, across territories, efforts should be made to engage and align major regulatory agencies (e.g., EMA and FDA) as early as possible.

Clinical studies – later phase clinical trials

The aim is to take forward drugs from early phase trials if supported by data, whilst postponing or discontinuing paediatric development of inactive drugs. With results from appropriately designed and conducted early phase clinical studies no further evaluation of some drugs will be required, whilst others should progress to evaluation of safety and efficacy, such as in randomised parallel-group or multi-arm, multi-stage later-phase clinical studies.

Ultimately, larger late-phase clinical studies will be required to demonstrate efficacy in the paediatric population. However, these studies should not be expected to be identical to those performed in adults. The number of paediatric/teenage patients with given target(s)/ disease(s) available for inclusion in such studies within a reasonable time frame must be borne in mind, and trial designs must be reconsidered and optimised for these rare population subgroups in the era of MoA-

based drug development. Randomized clinical trials are comparative in principle: the primary question, ‘‘can we identify person/people for whom this is the right treatment/drug?’’ is fundamentally different from asking which treatment performs better or best in the population overall and the latter, classical phase III approach may not answer the primary question.

Application of a MoA approach in *adolescents*

Historically patients <18 years have been excluded from adult clinical studies, even when the disease under investigation and the MoA of the drug under study would suggest this to be unnecessary. For example, although rare, adolescents may develop metastatic melanoma with a very poor prognosis (Berk 2010) and should not be refused access to trials with innovative compounds being developed for adults. There are currently four drugs with agreed PIPs for melanoma patients aged 12-18 years with 5-7-year timelines and study-end-dates ranging from 2017-2019, even though the drugs are authorised for their adult counterparts. Recruitment to most of the melanoma trials conducted for adolescents is slow, chiefly because of the rarity of the disease in this age group when considered in isolation, the off-label usage of these experimental drugs available to adults, and the rapid evolution of standards of care. In the future, it would seem sensible to include adolescents (from the age of 12 years) in early phase clinical studies and large pivotal trials currently only open to adult patients (18 years and above). They would still be cared for clinically by paediatric oncologists with age-specific expertise, even though the involvement of both adult and paediatric health professional as investigators might add complexity to such a trial. This approach would also be appropriate for other rare cancers and more generally in the teenage group of patients.

An example of MoA driven drug development

Inhibitors of BRAF have shown clinical value in the treatment of malignant melanomas. In addition BRAFV600 has been demonstrated to be an oncogenic driver in paediatric gliomas (Bautista 2014). There are two early-phase paediatric clinical studies of BRAF inhibitors – vemurafenib and dabrafenib – currently taking place (Bautista 2014, Kieran 2015). The development of dabrafenib is considered a paradigm for the MoA biology-driven approach by paediatric oncologists where the early phase clinical trial has focussed on common paediatric tumours, with an unmet

need for new drugs, where BRAF mutations are thought to play a major role in the pathogenesis. Complete and partial responses are being seen in BRAF mutated high-grade and low-grade gliomas (Keiran 2015), Although drugs targeting this mutation are relevant only for a subpopulation of patients, the disease represents a high unmet medical need and a difficult to treat disease in all patients.

Benefits and Challenges

A MoA biology-driven approach to drug development for paediatric cancers would support the objectives of all stakeholders by giving patients better access to potentially effective treatment underpinned by sound scientific knowledge and data. A greater number of potentially effective drugs would be evaluated more rapidly in paediatric early phase clinical studies and have the opportunity to reach front-line therapy more rapidly. For adolescents, integration with “adult” studies could mean better access to a wider range of therapeutic options earlier in treatment.

For companies developing drugs, this approach would provide a cooperative working model with advantages for all through shorter and more effective trials with a robust scientific approach, and better, faster recruitment of patients, enabling drugs to go from bench to bedside more quickly. On the regulatory side this may make for a clearer and more straightforward path to successful label updates.

To reap the benefits of a MoA approach, certain *challenges* must be overcome. The “rules of engagement” need to be defined; for example, that work in the pre-competitive space requires companies to share sensitive information, and that not all drugs will be studied at a phase III level and may be deprioritized, needs to be widely appreciated. Currently, no paediatric medicines legislation in the EU or elsewhere in the world has been substantially modernised, this has however been discussed by US legislators (Young 2015). In the EU, introducing such changes would facilitate prioritising the development of relevant oncology medicines for children by the Paediatric Committee. Finally there is a need for an open, public prioritization forum where all parties would regularly exchange information so as to allow for a timely updating of the life cycle of each drug/class of drug/disease area.

Conclusions

This strategy for MoA, biology-driven, paediatric oncology drug development will accelerate drug development and will enact groundbreaking changes in the delivery of precision medicines to children. The paradigm is to conduct early-phase paediatric studies, which efficiently evaluate drugs against targets identified in an aggregated database of paediatric tumour targets. This database has already been initiated by the ITCC. A number of PIPs have already been agreed on the basis of a proposed MoA approach. This will ultimately result in new drugs being introduced rapidly into front-line therapy, thereby increasing survival and reducing sequelae of therapy for children and young people with cancer.

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Conflicts of Interest

ADJP, CC, DB, JC, LC, BG, PK, LM, SMP, GS, CS, JS, HvdB, OW, KN and GV have nothing to declare.

RR and HC report to and are employees of F Hoffmann-La Roche Ltd, BG-B reports to and is an employee of Bristol Myers Squibb, RD reports to and is an employee of Novartis Pharma AG, JS reports to and is an employee of TetraLogic Pharmaceuticals and has been an employee of GSK and AstraZeneca and MU-F

reports to and is an employee of Boehringer-Ingelheim. RR is a shareholder of F Hoffmann-La Roche Ltd.

RH is a full-time employee of the European Medicines Agency, a decentralised agency of the European Union.

Figure 1

Information required to underpin selection of a paediatric MOA informed approach

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